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Evaluation a renal function of patients with Medication-overuse headache (MOH)

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Abstract

Excessive drug use causes Medication-overuse headache (MOH) which can be manifested with chronic daily headaches, occurring monthly 15 or more days when the medicament is used redundantly for more than three months. Recent studies concerning the epidemiology of drug-induced disorders suggest that an increased risk of nephrotoxicity appears in a group of patients who abuse NSAIDs. The aim is to confirm the early phase of nephrotoxicity in patients with (MOH), who were treated with NSAIDs in combination with other drugs (analgesics, triptans, and antidepressants) and compared patients treated only with Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen, and Celecoxib. Besides conventional markers of renal functioning (serum/urine creatinine determined by Jaffe methods, enzymatic assay for urea serum). Imunoturbodimetric assay for determination of urinary albumin, microalbuminuria, and β2-microglobulin will be used. Significant glomerular and tubular damage has been reported, and patients on combination therapy with NSAIDs and other drugs (analgesics, triptans, and antidepressants) have seen more glomerular changes than patients treated with NSAID monotherapy.

Keywords: Medication-overuse headache, Nephrotoxicity, Nonsteroidal antiinflammatory drugs

1.Introduction

Headache is one of the most common symptoms in the general population, as well as in medical practice in the world, with a prevalence of 8% in males and 12-15% in females. Migraine is the most common cause of headaches and contributes to a neurological disorder with a serious socio-economic burden. Migraine affects approximately 13% of adults in the United States, and its prevalence ranges between 12% and 20% in different countries in the world.

A special condition observed in chronic migraine patients, classified as Medication-overuse headache (MOH), is characterized by frequent intake of antimigraine drugs, is assumed to increase the frequency and intensity of headache [1]. The prevalence rate of chronic migraine (CM) in the general population is 2-4% [2]. Each year, approximately 2.5% of patients with migraine episodes (EM) develop a new-onset chronic migraine (CM). At this point, CM is the most important challenge for tertiary

headaches, where more than 50% of patients are referred to monitoring the chronic process and its possible complication with MOH [3]. Medication-overuse headache (MOH) can be manifested with chronic daily headaches, occurring monthly 15 or more days when the medicament is used redundantly for more than three months [4].

Despite the introduction of a new class of migraine-specific drugs with superior efficacy over 3 decades ago, triptans, nonsteroidal anti-inflammatory drugs -NSAIDs remain the most commonly used therapy for a migraine attack. Some groups are easily accessible and are usually much cheaper than triptans which contributes to their abuse [4]. NSAID- use in migraine is accompanied by their analgesic, anti-inflammatory, and antipyretic effects, supported by indirect evidence that prostaglandins are involved in the pathophysiology of migraine [5]. Schuh et al emphasize the importance of the cyclooxygenase system in the peripheral arm of the trigeminovascular system TGV and suggest that NSAIDs may be effective in the treatment of migraine by the action of these peripheral nociceptors [6]. Despite the many positive effects, however, NSAIDs do not meet the expected results [4]. William and co-workers have confirmed that inhibition of prostaglandin-mediated NSAID mediation prevents neurogenically mediated inflammation in the trigeminovascular system and the reduction of pain, but at the same time inhibiting prostaglandin in the kidney may reduce renal blood flow and glomerular filtration rate, thereby promoting sodium and water retention [6,7].

A recent epidemiological study on drug-related disorders has proven that excessive drug use can lead to nephrotoxicity and potential renal impairment [8, 9]. In particular, drug-related nephrotoxicity accounts for 18-27% of all acute kidney disorders in the United States and can affect all aspects and any part of the kidney structure from various mechanisms of renal dysfunction [4].

Many nephrologists report that NSAIDs have been classified into the second group for nephrotoxicity, after aminoglycosides as the cause of Akute kidney injury (AKI) [10]. Nephrotoxicity caused by NSAID includes the following stages of renal impairment: tubular necrosis, acute tubular nephritis, glomerulonephritis, renal papillary necrosis, chronic renal impairment, electrolyte, and water retention, hypertension, hyperkalemia, and hypoaldosteronism. However, more recent studies have summarized these enumerated phases in the following conditions: acute renal impairment, chronic renal impairment, interstitial nephritis, and subclinical nephrotoxicity [4, 11].

It is clear that NSAIDs are associated with all forms of renal impairment, but, however, if they are detected early, acute syndromes have a good prognosis. However, this assumption does not apply to chronic renal impairment [11, 12, 13].

The traditional laboratory analyses for the detection of renal impairment, which includes creatinine, creatinine clearance, urea, electrolytes, urine sediment, and radiological investigations, are not only sensitive and specific but do not allow early detection of renal impairment, cannot detect adequate differentiation between the various degrees of AKI and as such cannot be used as a signal for stopping therapy with drugs that exhibit strong nephrotoxicity [14]. In fact, until recently the rise in serum creatinine was widely considered to be the "gold standard" for detecting AKI, it is now clear that serum creatinine changes when 50% of renal function is lost. It is therefore very important, in addition to these parameters, to follow certain biomarkers, which were previously determined in vivo conditions on experimental animals and then used as modeling systems for the human organism [4, 15]. On the other hand, acute

renal impairment (AKI) and Chronic kidney disease (CKD) are conditions that significantly increase morbidity and mortality.

Although new biomarkers are used in practice, for the diagnosis of AKI and CKD it is still set with surrogate markers such as glomerular filtration rate (GFR), serum creatinine (SCr), urine excretion, and creatinine-based SCr scaling is limited as a marker of both renal dysfunction and settings and may be inaccurate in several situations. In some cases, serum Cr may increase in prerenal azotemia without tubular damage, as in patients with low muscle mass or with fluid and drug overload affecting serum Cr levels [16].

New biomarkers have the potential to identify previous patients with Akute kidney injury (AKI) and Chronic kidney disease (CKD) and potentially intervene in the future to modify results [17].

The aim is to confirm the early phase of nephrotoxicity in patients with Medication-overuse headache (MOH), that were treated with NSAIDs in combination with other drugs (analgesics, triptans, and antidepressants) and compared patients treated only with Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen and Celecoxib, all patients regardless the duration of therapy is compared with a control group.

2.Material and method

For the realization of the set, goals will use urine and venous blood from patients with chronic headache and migraine pains from the Clinic of Neurology –Tetovo (Polog Region of R.N.M), patients with normal renal function. Out of 96 patients, 12 patients have been treated for 10 years with Diclofenac duo 75 mg capsules, 12 patients with Paracetamol 500 mg tablets, treated for more than 5 years with occasional headaches (symptomatic). Patients who had a headache less than 15 days a month, of which 12 patients treated for 5 years with Ibuprofen 600 mg, 12 patients with Piroxicam 20 mg capsules for more than 5 to 10 years, 12 patients with Ketoprofen 100 mg tablets for up to 10 years and 12 patients with Celecoxib 200 mg. - treated for 12 months. And a special group of 24 patients with overdose headache -Medication-overuse headache (MOH) treated more than 15 days a month with combination therapy of NSAIDs + triptans + antidepressants. The average age of patients is 42.047±7.41 years, with a range of 35-65 years with a mean follow-up of up to 120±12.6 months, while the measurements were made in 2019, all patients regardless of the duration of therapy is compared with a control group of subjects (different in relation to the study region) with normal renal function.

Patients included in the examination were informed about the method of implementation and the purpose of the research before giving their written consent. They were also asked not to use any other medicines before taking the examinations. Patients with prior renal disease were excluded from the study. The examination was conducted according to the designed protocol, respecting the ethical principles of the Helsinki Declaration on Medical Research on People and Licenses from the Ethics Committee of the Faculty of Medical Sciences at the University "Goce Delcev" – Stip [18]. The results represent the average value of the three measurements, made under identical conditions. For the purpose of analysis, the sample was used 5 ml of blood, collected in special tubes, without anticoagulants. All materials for analysis are measured in the laboratories of Clinical Hospital in Tetovo [13].

To determine creatinine and specific biomarkers (β2M and microalbuminuria), the first-morning urine was used. The samples were processed according to the protocol described by Havziu et al. [19] and subsequently used for further biochemical characterization.

For testing the creatinine serum/urine, we used the Jaffe method - during the reaction of the creatinine with the basic reagents (Flex reagent cartridge), a complex of red color is formed which is followed by measuring the change of absorbance at a time interval of 510 nm (Dimension Rxl) [13].

Urea serum, the enzymatic-urea hydrolysis under the influence of the urease enzyme, the formed ammonia (NH_3) reacts with the catalytic effect of the Glutamate dehydrogenase stabilizers -GLDH (Flex Reagent Cartridge), α-ketoglutarate- α-KG (Flex Reagent Cartridge), and Nicotinamide adenine dinucleotide -NADH (Flex Reagent Cartridge). As a result of the reaction, glutamic acid and NAD are formed. The decrease in absorbance due to the reduced NADH oxidation is proportional to the release of the urea NH_3, measured at a value of 340 and 383 nm (Dimension Rxl) [13].

For the determination of urinary albumin, microalbuminuria, we used a visual Reading urine tape test in Combilyzer 13 - a test is based on the "protein error" principle of the indicator, which is caused by the presence of albumin. Sulfanephthalein has a high sensitivity to albumin. The color fields correspond to the following values: 10, 30, 80, and 150 mg/L urinary albumins.

For β2M determination imunonephelometry by BN II/BN ProSpec^R System was used [13].

3.Statistical data processing

Statistical data processing was performed in SPSS for Windows 23.0 statistical software. Shapiro-Wilks tests, as well as skewness and kurtosis measures, were used to test the normality of the data distribution. Nonparametric and parametric tests for independent samples (H Kruskal-Wallis test) and post - hoc (Mann-Whitney test), were used to compare the analyzed groups. The data of interest are shown in tables and graphs. P values <0.05 were considered statistically significant.

4.Results and discussion

Results of comparison the values of the control group with of all treated patients with different groups of NSAIDs (Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen, Celecoxib and patients with MOH treated with NSAIDs in combination with other drugs (analgesics, triptans, and antidepressants) in terms of mean and mean values of the analyzed parameters regardless of the duration of therapy and the mechanism of action based on COX inhibition, significant differences were detected except for urea (serum) values presented in Table 1

Table 1. Values of Urea (serum) in patients treated with different groups of #NSAIDs and patients with combined therapy * compared with the control group of examinees, compared based on the median and mean values.

Group	**(Urea (serum) mmol/L)**			**p-level**
	mean ± SD	**min-max**	**median (IQR)**	
Control group compared to:	4.58 ± 0.9	2.5 – 6.6	4.45(4.1–5.1)	
Diclofenac	5.40 ± 1.6	2.9 – 8.4		[a]p=0.012 sig
Piroxicam	4.52 ± 1.1	3.1 – 6.5		[a]p=0.84 ns
Ketoprofen	5.70 ± 1.5	3.5 – 8		[a]p=0.0005 sig
Paracetamol	4.28 ± 1.1	2.5 – 6.3		[a]p=0.31 ns
Combination therapy*	5.14 ± 1.6	2.8 – 7.5		[a]p=0.049 sig
Ibuprofen	4.33 ± 0.3		4.15(4.12–4.7)	[b]p=0.44 ns
Celecoxib	6.26 ± 0.6		6.4(6.3–6.6)	[b]p=0.000001 sig

[a](t – test)[b](Mann-Whitney test)

#Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen, Celecoxib

*NSAIDsin combination with other drugs (analgesics, triptans and antidepressants)

The results presented in Table 1 show that serum urea concentrations were significantly lower in healthy subjects compared with patients receiving Diclofenac (4.58 ± 0.9 vs 5.40 ± 1.6; p = 0.012), Ketoprofen (4.58 ± 0.9 vs 5.70 ± 1.5; p = 0.000).), combination therapy * (4.58 ± 0.9 vs 5.14 ± 1.6; p = 0.049) and Celecoxib (4.45 vs. 6.4; p = 0.000001), and are of great clinical significance and suggest that with long-term use of Diclofenac, Ketoprofen and Celecoxib, as well as the combination of NSAIDs with other drugs (analgesics, triptans, and antidepressants) in the treatment of migraine headaches, result in a significant increase in serum urea except in patients treated with Piroxicam and Ibuprofen. The results obtained correspond to the results of [20] where, Diclofenac, Piroxicam, and Ibuprofen proved to be intermediate (between Aspirin and Indomethacin) in their relative capacity for acute renal impairment [20]. On the other hand, [21] with the latest research showed that the level of urea in the blood differs inversely from the speed of glomerular filtration, which may be falsely increased in subjects with a diet with protein, glucocorticoid therapy, tissue disorders, gastrointestinal bleeding, total parenteral nutrition or in chronic liver disease due to

decreased urea production. This fact indicates that NSAIDs, as cyclooxygenase inhibitors and combination therapy *, do not increase the value of degradation products (urinary creatinine). This means that no changes in renal function have been detected, correlating with the results of Prasad et al., That creatinine in serum and urine changes when already 50% of renal function is impaired [16].

The effects of NSAIDs on glomerular and tubular function are of great clinical and pathological significance and should therefore be monitored by more sensitive methods and biomarkers, which are presented in Tables 2 and Figure 1.

Table 2. Values of Microalbuminuria in patients with different groups of #NSAIDs and patients with Combined therapy* in comparison with the control group examinees based on median and mean values

Group	**(Microalbuminuria)**		**p-level**
	mean ± SD	**median (IQR)**	
Control group compared to:	10.25 ± 2.2	10 (10 – 10)	
Diclofenac	13.33 ± 7.8	10 (10 – 10)	p=0.39 ns
Piroxicam	20.0 ± 10.4	20 (10 – 30)	p=0.0067 sig
Ketoprofen	33.33 ± 23.5	30 (20 – 30)	p=0.00039 sig
Paracetamol	11.67 ± 5.8	10(10–10)	p=0.69 ns
Combination therapy*	47.37 ± 42.1	30(30–80)	p=0.0000 sig
Ibuprofen	16.67 ± 9.8	10(10–30)	p=0.07 ns
Celecoxib	13.33 ± 7.8	10(10–10)	p=0.39 ns

p (Mann-Whitney test)
[a](t-test)[b](Mann-Whitney test)
*Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen, Celecoxib
#NSAID in combination with other drugs (analgesics, triptans, and antidepressants)

According to the results shown in Table 2 in the monitoring of Microalbuminuria, showed significantly different values of albumin excretion in the urine of healthy subjects, and patients receiving Piroxicam (p = 0.0067), Ketoprofen (p = 0.00039), and combined therapy with NSAIDs, (p <0.0001). Microalbuminuria presented significantly lower values in healthy subjects compared with patients on chronic therapy with Piroxicam, Ketoprofen, and NSAIDs in combination with other drugs (analgesics, triptans, and antidepressants) —median 10, 20, 30, and 30, respectively. Based on the monitoring of microalbuminuria (as a marker for early identification of renal damage at the glomerular level), early changes at the glomerular level have been identified. This fact is a key fact, as it confirms once again the high sensitivity of microalbuminuria to identify small changes in GFR caused by nephrotoxic agents, that is, combination therapy*. These results correspond to the claims of Pedersen et al., That the biomarker microalbuminuria is a more sensitive indicator for the identification of renal dysfunction, as opposed to the monitoring of other urinary enzymes. The results are consistent with recent studies by Havziu., which confirmed previous preconceptions about the possibility of drug-induced nephrotoxicity in patients with MOH, particularly

NSAID abuse and combination analgesic therapy [4]. Numerous clinical trials have shown similar results at relatively low doses of Ketoprofen, Indomethacin and Diclofenac, with decreased renal clearance and varying levels of toxicity [22, 23, 24].

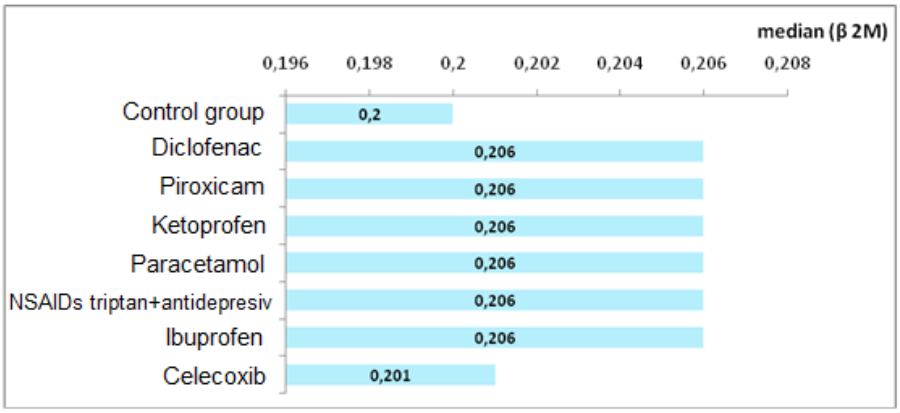

Figure 1. Values of β – 2M in patients with different groups of #NSAIDs and patients with Combined therapy * compared with a control group of examinees
*Diclofenac, Piroxicam, Ketoprofen, Paracetamol, Ibuprofen, Celecoxib
#NSAID in combination with other drugs (analgesics, triptans, and antidepressants)

A According to the results shown in Figure 1 β - 2 microglobulin (β 2M), showed significantly higher values in patients treated with Diclofenac, Piroxicam, Ketoprofen, Paracetamol, NSAIDs in combination with other drugs (analgesics, triptans, and antidepressants). who received Ibuprofen compared with healthy subjects ($p < 0.001$). The median of β - 2 microglobulins, ie the mean value of this parameter was 0.206 in all these groups of patients with headaches and migraine attacks, compared to 0.2 in the control group except in a group of patients treated with Celecoxib. From a clinical biochemical point of view, this fact indicates that COX1 inhibitors and combination therapy * significantly affect proximal tubular epithelial changes, which is reflected by increased urinary excretion of β2M (early markers of tubular dysfunction). Increased urinary excretion of β2M confirms identified changes in reabsorption and catabolism in the proximal tubules. The results obtained correspond to Ishioka T (1988) who proved that the administration of COX1-NSAID inhibitors (Sulindac) resulted in a significant increase in BUN and β -2M concentrations, but no significant change in serum creatinine, unlike tiaprophenic acid - Ketoprofen (did not result in significant changes in any of the parameters.

5. Conclusion

Significant glomerular and tubular damage has been reported, and patients on combination therapy with NSAIDs and other drugs (analgesics, triptans, and

antidepressants) have seen more glomerular changes than patients treated with NSAID monotherapy.
Confirmed sensitivity of specific bioindicators to detect early stage of nephrotoxicity at glomerular level – microalbuminuria, as well as at tubular level - and β2M has been demonstrated in the treatment of patients the long-term use of NSAIDs, as well as the combination of NSAIDs with other drugs (analgesics, triptans, and antidepressants) in the treatment of migraine headaches.

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